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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,243	08/27/2001	James R. Baker JR.	UM-06609	6118

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EXAMINER	
BARHAM, BETHANY P	
ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/940,243	BAKER, JAMES R.	
	Examiner	Art Unit	
	BETHANY BARHAM	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/21/09*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-46 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-46 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/6/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the Applicants' Response and Terminal Disclaimer filed on 1/21/09. Claims 26-46 and 53 are pending in this action. Claims 26-46 and 53 are rejected.

The terminal disclaimer filed on 1/21/09 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US 6,471,968 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Applicants Arguments with respect to the art were not persuasive and the previous rejections of record are hereby maintained.

MAINTAINED REJECTIONS

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 26-35 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., *Angew. Chem. Int. Ed. Engl.* 29 (1990) p.138-175 (herein referred to

as Tomalia et al) and Zhuo et al, J. of Controlled Release (1999), in view of Malik et al., Proceed. Int'l. Symp. Control. Rel. Bioact. Mater., 24 (1997) p. 107-108.

- Tomalia et al is taught above and teaches numerous functional groups attached to PAMAM dendrimers of various generations. Tomalia et al also teaches various NH2-terminated dendrimers reacted with either inorganic or organic acids and PAMAM dendrimer complexes formed from reactions with metals (p. 163-4, section 9.2.1-9.2.2). Tomalia et al teach conjugation of dendrimers to dopamine and catechol to act as targeting agents to increase ligand concentrations and conjugations to monoclonal antibodies for therapeutic and diagnostic purposes (p. 166-167, sections 9.2.5-9.2.6).
- Tomalia et al does not teach acylation of dendrimers, only functionalization.
- Zhuo et al teaches that functionalizing dendrimers with various end groups that can be linked to other chemical moieties and enhance surface properties of dendrimers for drug carriers and gene transfer agents is well known in the art. Zhuo et al specifically teaches acylation of dendrimers with acetic anhydride, which allows the dendrimer to become water soluble and further linked to an active agent such as fluorouracil, with potential for a carrier as an antitumor drug (pg. 254-255, Conclusion).
- Tomalia et al and Zhuo et al do not teach chemotherapeutic agents such as the platinum complex, cisplatin.
- The limitation of claim 32 is taught by Malik et al, who teaches that PAMAM dendrimers conjugated to the anti-tumor agent and platinum complex, cisplatin to

form a dendrimer-Pt complex. The dendrimer-Pt complex was found to be effective in reducing toxicity and increasing water solubility of cisplatin, while still maintaining anti-tumor activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the chemotherapeutic agent, cisplatin into a PAMAM dendrimer with the functional groups as described by Tomalia et al and Zhuo et al, since Tomalia teaches dendrimer metal complexes and Zhuo et al teaches complexes with reduced toxicity active agents such as fluorouracil (which has antitumor activity and normally has high toxic side effects). One of ordinary skill in the art would be motivated by the success of the results of Malik et al who found that the complexed dendrimer-Pt also reduces toxicity and increases solubility of cisplatin to combine with the teachings of Tomalia et al. Thus, it would have been *prima facie* obvious to combine the teaches of Malik et al with Tomalia et al and Zhuo et al to obtain a drug containing dendrimer with the functional group of choice.

Claims 26-27 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., *Angew. Chem. Int. Ed. Engl.* 29 (1990) p.138-175 (herein referred to as Tomalia et al) and Zhuo et al, J. of Controlled Release (1999), in view of US 5,714,166 (herein referred to as '166).

- Tomalia et al is taught above, but does not teach fluorescent agents, specifically fluorescein isothiocyanate.

- Zhuo et al is taught above, and teaches fluorescent agents such as fluorescein but not fluorescein isothiocyanate.
- The limitations of claims 36-37 are taught in '166. The conjugation of one or more functional groups (targeting and imaging agents) into dendrimers is taught. Specifically, example NN (col. 71 lines 40-42 and col. 72 lines 47-65) and example 29 (col. 91 line 9 – col. 92 line 14) teach preparation of PAMAM dendrimers conjugated to fluorescein isothiocyanate for imaging and various targeting agents.

It would have been obvious to one of ordinary skill in the art at the time the invention was made desiring to functionalize the surface of PAMAM dendrimers of various generations (G0-G9) to look to Tomalia et al. Tomalia et al teaches adding functional groups to the surface to change the surface charge. One of ordinary skill in the art would be motivated to obtain a neutral surface that would be less reactive with biological compounds to look for a functional group that would impart the neutral charge and increase water solubility, such as the acetyl group as taught by Zhuo et al. It would have been *prima facie* obvious to one of ordinary skill in the art that since PAMAM dendrimers are non-toxic and useful for specific delivery of imaging and targeting agents, and Zhuo et al teaches that acylation and linkage to fluorescein is also non-toxic and useful for imaging, to look to the teachings '166 (the conjugation of PAMAM dendrimers to targeting and imaging agents, specifically fluorescein isothiocyanate) in conjunction with Tomalia et al and Zhuo et al to obtain an acetylated PAMAM dendrimer for use in targeting and imaging in vitro.

Claims 26-46 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., *Angew. Chem. Int. Ed. Engl.* 29 (1990) p.138-175 (herein referred to as Tomalia et al) and Zhuo et al, J. of Controlled Release (1999), in view of US 5,714,166 ('166) and US 6,221,959 ('959).

- Tomalia et al is taught above, and teaches numerous functional groups attached to PAMAM dendrimers of various generations and targeting agents to increase ligand concentrations and conjugations to monoclonal antibodies for therapeutic and diagnostic purposes.
- Zhuo et al is taught above, and teaches fluorescent agents such as fluorescein but not fluorescein isothiocyanate.
- Tomalia et al and Zhuo et al do not teach fluorescein isothiocyanate or folic acid.
- The limitations of claims 36-37 are taught in '166. The conjugation of one or more functional groups (targeting and imaging agents) into dendrimers is taught. Specifically, example NN (col. 71 lines 40-42 and col. 72 lines 47-65) and example 29 (col. 91 line 9 – col. 92 line 14) teach preparation of PAMAM dendrimers conjugated to fluorescein isothiocyanate for imaging and various targeting agents.
- The limitations of claims 36-37 are taught in '959. '959 teaches that the dendrimers of Tomalia et al (polyamidoamines or polypropylimines of various generations) can be used in the complex and that various targeting agents to enhance binding, transport, etc. and include antibodies, ligands such as folic

acid, etc. can be incorporated (col. 9, lines 54-18 and col. 19, lines 5-24). '959 teaches that these complexes can be covalently modified (to incorporate groups including lipophilic groups, photo-induced crosslinking groups, alkylating groups, organometallic groups, intercalating groups, lipophilic groups, biotin, fluorescent and radioactive groups) and also teaches an Example 39 with of a complex with fluorescein isothiocyanate (col. 16, lines 27-35).

It would have been obvious to one of ordinary skill in the art at the time the invention was made desiring to functionalize the surface of PAMAM dendrimers of various generations (G0-G9) to look to Tomalia et al. Tomalia et al teaches adding functional groups to the surface to change the surface charge. One of ordinary skill in the art would be motivated to obtain a neutral surface that would be less reactive with biological compounds to look for a functional group that would impart the neutral charge and increase water solubility, such as the acetyl group as taught by Zhuo et al. It would have been *prima facie* obvious to one of ordinary skill in the art that since PAMAM dendrimers are non-toxic and useful for specific delivery of imaging and targeting agents, and Zhuo et al teaches that acylation and linkage to fluorescein is also non-toxic and useful for imaging, to look to the teachings '166 and '959 (the conjugation of PAMAM dendrimers to targeting and imaging agents, specifically fluorescein isothiocyanate) in conjunction with Tomalia et al and Zhuo et al to obtain an acetylated PAMAM dendrimer for use in targeting and imaging in vitro. '959 also teaches that a the dendrimers of Tomalia et al can be used in their invention and further that targeting agents such as folic acid are used to increase ligand concentrations. As such one of

ordinary skill in the art would have a reasonable expectation of success in formulating a dendrimer of Tomalia et al that has been acetylated according to Zhuo et al to decrease the toxicity of various anti-tumors and fluorescent agents such as fluorescein isothiocyanate as taught by '166 and '959, and further incorporating a targeting agent to increase ligand concentrations as taught by Tomalia et al such as folic acid of '959.

Response to Arguments

Applicant's arguments with respect to claims 26-46 and 53 have been considered but not persuasive. Applicant argues that the art does not teach acetylation of dendrimers wherein greater than 80% of the primary amino groups of the dendrimer are acetylated, and the Examiner has used improper hindsight reconstruction. As taught above, Tomalia et al in view of Zhuo et al teach functional groups attached to PAMAM dendrimers of various generations, Tomalia et al gives a generic teaching of functionalization while Zhuo et al teaches that many functional end groups may be attached to vary the surface properties of the dendrimer and is specifically relied upon to show the acylation of the generation 4 and 5 dendrimer with acetic anhydride (which is how the instant specification also produces an acylated G5 dendrimer) which has been further conjugated to 5FU (see 2.4 preparation of dendrimer-5FU conjugates and 2.4.1 Acetylation of generation 4 and 5 pg. 251 and pg. 254). Zhuo et al teaches that such a functionalization results in the dendrimer becoming water soluble, and then further when linked with 5FU reduces toxicity of the compound and useful in anti-tumor drugs. The Zhou reference is good for all its teachings and nothing in the reference

indicates only 50% can be acylated, rather a single example disclosed in Zhou teaches 50% and therefore suggests acylation is a results effective parameter that one of ordinary skill in the art would know how to modify. Since Zhuo teaches adding acetic anhydride to a G5 dendrimer in order to yield a acylated dendrimer, the product would be the same as instant claimed as the acetic anhydride would react with any available amino groups on the dendrimer and absent a showing by Applicant that 80% or greater is unexpected, the rejection above is maintained and obvious over the instant claims. Malik is then relied upon to show that dendrimer complexes with anti-tumor such as cisplatin is known and reduces toxicity and that the combined art would be successful not only in reducing toxicity but making a neutralized water soluble acetylated G5 dendrimer for linking antitumors and/or fluorescing/imaging agents (Tomalia, Zhuo and Malik or '166 and/or '959). Tomalia generically teaches including targeting agents with dendrimers of various generations while Zhuo teaches linking fluorescent agents to acetylated G5 dendrimers, and '166 teaches PAMAM dendrimers conjugated to fluorescein isothiocyanate for imaging and various targeting agents, while '959 teaches fluorescein isothiocyanate and further targeting agents such as folic acid for increasing ligand concentrations using the dendrimers of Tomalia et al.

The Examiner also respectfully points out that the Applicant bears the greater burden to show non-obviousness. According to MPEP 2113: "The Patent Office bears a lesser burden of proof in making out a case of *prima facie* obviousness for product-by-process claims because of their peculiar nature" than when a product is claimed in the conventional fashion. *In re Fessmann,* 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA

1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi,* 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983)".

The Examiner respectfully reminds Applicants that the person of ordinary skill in the art probably possesses a PhD and publishes in peer-reviewed scientific journals and that such a combination of references is not the result of hindsight reconstruction but rather the natural progression of reading the available art.

- Tomalia teaches functionalizing a dendrimer of various generations is known, and that various targeting agents can be attached,
- while Zhuo et al teaches making water soluble acetylated G5 dendrimers of Tomalia which are also conjugated to fluorescent agents and also anti-tumors reduce their toxicity;
- while Malik teaches the specific anti-tumor has reduced toxicity when complexed with a dendrimer;
- while '959 references dendrimers of Tomalia et al with targeting agents of folic acid and/or conjugated with fluorescein isothiocyanate;
- '166 also teaches preparation of PAMAM dendrimers conjugated with fluorescein isothiocyanate.

Applicant's argue that the art teaches 'reactive' dendrimers with "varied hydrophobicity", however Tomalia teaches numerous examples of the functionalization

of dendrimers of various generations resulting in anionic surfaces, cationic surfaces, chiral surfaces, hydrophobic surfaces, and water-soluble dendrimers (pg. 165, col. 1, lines 6-15) which can be further conjugated to various targeting agents; while Zhuo et al teaches that acetylation of a G5 dendrimer results in a water-soluble dendrimer that includes various non-toxic conjugated moieties (fluorescein and anti-tumors) and the remaining art teaches specific examples of fluorescent agents, anti-tumors and targeting agents that can be conjugated to the dendrimers of Tomalia. As such it would be obvious to combine Tomalia and Zhuo in view of Malik or '166 or '166 and '959.

The Examiner notes that Applicant has amended claim 26 from a product to a product-by-process claim. MPEP 2113 states: "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted)"... "[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section

102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972). The Examiner maintains that such a combination of Tomalia and Zhuo in view of Malik or '166 or '166 and '959 is obvious and the burden now shifts to the Applicant to provide facts, evidence, statistical results, showing that the instant invention is not obvious over the prior art.

Conclusions

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BETHANY BARHAM whose telephone number is (571)272-6175. The examiner can normally be reached on M-F from 8:30am to 5pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bethany Barham
Examiner-1615

/Michael P Woodward/
Supervisory Patent Examiner, Art Unit 1615